Is prenatal testesterone estrogen balance related to smoking addiction?

Addiction and 2D:4D

Hümeyra Yaka[1], Selma Pekgör[2], Haluk Yaka[3], Mustafa Özer[3]
[1] Department of Family Medicine, Family Health Center Number 48
[2] Department of Family Medicine, Konya City Hospital
[3] Department of Orthopaedics and Traumatology, Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

Abstract

Aim: The 2D:4D ratio, which is the ratio of the length of the index finger to the length of the ring finger, is negatively correlated with prenatal exposure to testosterone. The aim of this study was to investigate the relationship between 2D:4D ratio and smoking addiction.

Material and Methods: 81 patients who were admitted to the orthopaedics and traumatology outpatient clinic and who had smoking addiction were included in the study. 102 patients without a history of smoking addiction were determined as the control group. The second and fourth finger lengths of both groups were measured. The data obtained from both groups were compared statistically.

Results: Mean left hand and right hand 2D:4D ratios was significantly lower in patients with smoking addiction compared to the control group (P<0.001, P=0.03 respectively). Both left hand and right hand 2D:4D ratios were significantly lower in male smokers than in male controls (P<0.001, P=0.007 respectively). Left hand 2D:4D ratio was significantly lower in female smokers than in the female control group, while there was no significant difference between right hand 2D:4D ratio (P<0.001, P=0.113 respectively).

Discussion: Low 2D:4D ratio, which is an indicator of high testosterone exposure in the prenatal period, seems to be associated with smoking addiction. The 2D:4D ratio may be useful in assessing the risk of smoking addiction in individuals in childhood and adolescence. Knowing that individuals with low 2D:4D have a higher addiction potential may be useful in addiction prevention and addiction treatment.

Keywords

Smoking Addiction, 2D:4D Ratio, Testosterone, Estrogene

Introduction

The 2D:4D ratio, which is an indicator of prenatal testosterone-estrogen balance, is the ratio of the length of the second finger (index finger) to the length of the fourth finger (ring finger) [1, 2]. The 2D:4D ratio stabilises in the 2nd year of life, then remains constant throughout life and is inversely correlated with intrauterine testosterone exposure, i.e. a low 2D:4D ratio is indicative of higher fetal testosterone exposure [2]. It has been shown that the 2D:4D ratio, which indicates intrauterine testosterone-estrogen balance, is inversely correlated with testosterone level in adulthood [3, 4]. Associations of 2D:4D ratio with breast cancer, prostate cancer, obesity, and osteoarthritis have been shown [5-8]. Associations of 2D:4D with the skeletal system, such as proximal tibia morphology, scapula morphology and developmental hip dysplasia, have also been demonstrated [9-11].

Han et al. investigated the relationship between alcohol dependence and 2D:4D ratio and found a significant relationship between alcohol dependence and low 2D:4D ratio [12]. Lenz et al. showed a significant association between patients with a low 2D:4D ratio who had been exposed to higher testosterone during the prenatal period and increased alcohol deprivation. [13]. It has also been shown that low 2D:4D is associated with increased impulsivity and aggression [14]. However, to the best of our knowledge, the relationship between smoking addiction and prenatal testosterone estrogen balance has not been investigated yet. The aim of this study was to investigate whether there is a relationship between smoking addiction and prenatal testosterone estrogen dependence. Our hypothesis is that high prenatal testosterone exposure (low 2D:4D) may be associated with smoking addiction.

Material and Methods

Between January 2023 and July 2023, 81 patients with cigarette addiction who were admitted to the orthopaedics and traumatology outpatient clinic of Necmettin Erbakan university medical faculty for only minor trauma without any fracture or ligament damage and who did not require surgery were included in the study. The inclusion criteria were that the patients were regular smokers, had not quit smoking after a successful smoking cessation treatment, had a smoking burden of at least one year/pack of smoking and showed behaviours showing deprivation symptoms when they did not smoke [15]. Exclusion criteria were any substance addiction other than smoking, history of psychiatric illness or psychiatric treatment, previous hand surgery, hand deformities and metabolic bone diseases. In accordance with the age and gender of the patients included in the study, 102 patients who were admitted to the orthopaedics and traumatology outpatient clinic only for minor trauma and who had no history of smoking addiction in any period of their lives were determined as the control group.

Data collection

The lengths of the second and fourth fingers were measured by 1 of the authors (H.Y.) using a calliper with a sensitivity of 0.01 mm on the palmar side of the hand between the fingertip and the basal crease at the level of the metacarpophalangeal joint. Care was taken to distinguish regular wrinkles from irregular wrinkles or secondary wrinkles in soft tissue, because irregular wrinkles are formed later than regular wrinkles, after the 11th week of the intrauterine period, by disruption of the dermal surface due to the onset of finger flexion.[10]. The lengths of the second and fourth fingers measured in both hands were recorded.

Statistical analysis

Data were analysed using SPSS software (IBM-SPSS 22.0). Descriptive statistics and frequency analysis were used for descriptive analyses. The normality of the data was analysed by Shapiro-Wilk test. Mann Whitney-U and T-testwere used for comparison of independent variables.

Ethical approval

This study was approved by the Ethics Committee of Necmettin Erbakan University, Faculty of Medicine (Date: 2024-07-06, No:2024-5030).

Results

Of the 81 patients with smoking addiction, 55 were male and 26 were female, while 70 of the 102 patients in the control group were male and 32 were female, and there was no significant difference between the two groups in terms of gender (P=0.886) (table 1). The mean age of the patients with smoking addiction was 35.96±12.7, while the mean age of the control group was 36.2±10.7 and there was no significant difference between the groups (P=0.910) (table 1). The mean smoking burden of the smoking patients was 27.8±23.3 pack-years. The mean left hand 2D:4D ratio was 0.95±0.03 in patients with smoking addiction and 0.98±0.03 in the control group, and the left hand 2D:4D ratio was significantly lower in patients with smoking addiction (P<0.001). The mean right hand 2D:4D ratio was 0.98±0.04 in patients with smoking addiction and 0.96±0.03 in the control group, and the right hand 2D:4D ratio was significantly lower in patients with smoking addiction (p=0.003) (table 2). When the groups were divided according to gender, left hand 2D:4D ratio was significantly lower in male patients with smoking addiction compared to male patients in the control group (P<0.001). Right

Table 1. Demographic characteristics of the patients

	Group with smoking addiction	Control group	P value
Number of patients (n)	81	102	
Age (year±SD)	35,96±12,7	36,2±10,7	0.886
Gender (M/L)(%)	55 (67,9) / 26 (32,1)	70 (68,6) / 32 (31,4)	0.910
Pack-year	27.8±23.3		

Table 2. Comparison of the groups in terms of 2D:4D ratio

		Group with smoking addiction	Control group	P value
General	Left 2D:4D (mean±SD)	0.95±0.03	0.98±0.03	P<0.001
	Right 2D:4D (mean±SD)	0.98±0.04	0.96±0.03	p=0.003
Male	Left 2D:4D (mean±SD)	0.96±0.03	0.98±0.04	P<0.001
	Right 2D:4D (mean±SD)	0.95±0.03	0.98±0.04	P=0.007
Female	Left 2D:4D (mean±SD)	0.96±0.02	0.99±0.03	P<0.001
	Right 2D:4D (mean±SD)	0.96±0.03	0.97±0.04	P=0.113

hand 2D:4D ratio was significantly lower in male patients with smoking addiction compared to male patients in the control group (P=0.007). Left hand 2D:4D ratio in female smokers was significantly lower than in female control group (P<0.001). there was no significant difference between right hand 2D:4D ratio of female smokers and right hand 2D:4D ratio of female control group (P=0.113) (table 2).

Discussion

The most important finding of this study is that there is an association between smoking addiction and low 2D:4D ratio, which is an indicator of high testosterone exposure in the prenatal period.

The biology of nicotine addiction and its effects on the body are complex [16]. Nicotine causes stimulation of nicotinic cholinergic receptors in the brain, resulting in the release of various neurotransmitters [16]. Dopamine, one of these neurotransmitters, creates a pleasurable experience in the body. Nicotine interacts with many complex chemical pathways in the brain, giving the user pleasure and reducing stress and anxiety. Smoking improves mood, concentration and performance of certain functions[16] Quitting smoking causes deprivation symptoms, such as irritability, depressed mood, restlessness and anxietyJoyve et al. showed that patients presenting with boxer's fracture (distal fracture of the fifth metacarpal due to punching) had a lower 2D:4D ratio than the control group and showed that aggression and aggressiveness were associated with a low 2D:4D ratio [17]. Considering that previous studies have shown that low 2D:4D ratio, which is an indicator of high testosterone exposure in the prenatal period, is associated with irritability, aggression, aggressiveness and impulsivity, the relationship between low 2D:4D ratio and smoking addiction can be explained in two ways. The first is that smokers who are addicted to cigarettes have increased anxiety, increased stress and irritability, which are associated with a low 2D:4D ratio, they may benefit more from the mood-enhancing effects of smoking through the dopaminergic system and therefore their smoking dependence may be high for this reason. The second way is that users with a low 2D:4D ratio may experience nicotine deprivation symptoms more severely than normal and therefore may not be able to quit smoking, but we have no data on this issue and further studies are needed to evaluate the effectiveness of smoking addiction treatment with a low 2D:4D ratio.

Smoking continues to be one of the leading causes of preventable disease and death [16]. Smoking usually starts in childhood and adolescence and four-fifths of all smokers have experimented with cigarettes by the age of 18 [16]. Two thirds of young people try smoking, but 20 to 25 per cent of them become addicted in adulthood [16]. The known risk factors for this group of 20-25% who become addicted after trying cigarettes are low school success, rebelliousness, increased stress, anxiety and risk taking [16]. It is known that smoking addicts become addicted because they benefit from nicotine's effect of improving mood, reducing stress and increasing concentration and attention, while low 2D:4D ratio is associated with aggression, aggression, stress and anxiety, so the fact that smoking addicts have low 2D:4D ratio supports each other. In

our study, a significant relationship between low 2D:4D ratio and smoking addiction was shown, which complements and strengthens these relationships reported in the literature, and to the best of our knowledge, this relationship has not been previously investigated in the literature. We believe that this study is a pioneering study for future studies that will investigate the relationship between 2D:4D ratio and the potential to become addicted to smoking, evaluate the relationship between 2D:4D ratio and the success of smoking addiction treatment, and investigate the relationship between 2D:4D ratio and smoking addiction level.

Limitation

This study had some limitations. These limitations were that it was not known whether the patients who were addicted to smoking had a previous desire to quit smoking and their level of smoking addiction.

Conclusion

Low 2D:4D ratio, which is an indicator of high testosterone exposure in the prenatal period, seems to be associated with smoking addiction. The 2D:4D ratio, which is stabilised from the 2nd year after birth, may be useful in assessing the risk of smoking addiction in individuals in childhood and adolescence. Knowing that individuals with low 2D:4D have a higher addiction potential may be useful in addiction prevention and addiction treatment.

References
1. Özer İ, Temiz SA, Ataseven A, Dursun R, Uyar M, Özer M. Is prenatal testosterone-estrogen balance associated with psoriasis?. Dermatol Ther. 2020;33(6):e14213.
2. Kasielska-Trojan A, Sitek A, Gabryszewski M, Antoszewski B. Digit ratio and the femoral circumflex artery perforator: A sex-dependent association between the vascular system of the thigh and prenatal sex hormones?. Early Hum Dev. 2024;188:105901.
3. Manning JT, Fink B. Sexual dimorphism in the ontogeny of second (2D) and fourth (4D) digit lengths, and digit ratio (2D:4D). Am J Hum Biol. 2018;30(4):e23138.
4. Coco M, Perciavalle V, Maci T, Nicoletti F, Di Corrado D, Perciavalle V. The second-to-fourth digit ratio correlates with the rate of academic performance in medical school students. Mol Med Rep. 2011;4(3):471-476.
5. Manning J, Leinster S. Re: The ratio of 2nd to 4th digit length and age at presentation of breast cancer: a link with prenatal oestrogen?. The Breast. 2001;4(10):355-357.
6. Jung H, Kim KH, Yoon SJ, Kim TB. Second to fourth digit ratio: A predictor of prostate-specific antigen level and the presence of prostate cancer. BJU Int. 2011;107(4):591-596.
7. Fink B, Manning JT, Neave N. The 2nd–4th digit ratio (2D: 4D) and neck circumference: implications for risk factors in coronary heart disease. Int J Obes (Lond). 2006;30(4):711-714.
8. Zhang W, Robertson J, Doherty S, Liu J, Maciewicz R, Muir K, et al. Index to ring finger length ratio and the risk of osteoarthritis. Arthritis Rheum. 2008;58(1):137-144.
9. Kaya O, Gonder N, Demir DA, Demir IH, Akay O. Patients with developmental dysplasia of the hip shows higher digit ratio (2D: 4D). Early Hum Dev. 2023;185:105857.
10. Yaka H, Baako Y, Özer M, Kanatli U. Is prenatal testosterone-estrogen balance

related to critical shoulder angle?. Early Hum Dev. 2023;187:105890.

11. Yaka H, Özer M. Is the ratio of the index to ring finger length, a potential marker for prenatal testosterone-estrogen balance, related to posterior tibial slope?. Knee. 2023;43:200-207.

12. Han C, Bae H, Lee Y-S, Won S-D. The ratio of 2nd to 4th digit length in Korean alcohol-dependent patients. Clin Psychopharmacol Neurosci. 2016;14(2):148.

13. Lenz B, Mühle C, Braun B, Weinland C, Bouna-Pyrrou P, Behrens J, et al. Prenatal and adult androgen activities in alcohol dependence. Acta Psychiatr Scand. 2017;136(1):96-107.

14. Cicek IE, Cicek E, Demirel B, Ayhan MG, Varsak N, Özbek SY, et al. Digit ratio (2D: 4D), impulsiveness and aggression in male heroin addicts: a prospective controlled study. Pers Individ Diff. 2017;117:1-5.

15. Mitchell JT, McClernon FJ, Beckham JC, Brown RA, Lejuez CW, Kollins SH. Smoking abstinence effects on emotion dysregulation in adult cigarette smokers with and without attention-deficit/hyperactivity disorder. Drug Alcohol depend. 2019;205:107594.

16. Benowitz NL. Nicotine addiction. N Engl J Med. 2010;362(24):2295-2303.

17. Joyce C, Kelly J, Chan J, Colgan G, O'Briain D, Mc Cabe J, et al. Second to fourth digit ratio confirms aggressive tendencies in patients with boxers fractures. Injury. 2013;44(11):1636-1639.